COMPARISON OF FONDAPARINUX AND ENOXAPARIN IN NON-ST ELEVATION ACUTE CORONARY SYNDROME

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF DM – BRANCH II CARDIOLOGY EXAMINATION OF THE TAMILNADU DR. MGR MEDICAL UNIVERSITY, CHENNAI, TO BE HELD IN JULY/AUGUST 2009.

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "COMPARISON OF FONDAPARINUX AND ENOXAPARIN IN NON-ST ELEVATION ACUTE CORONARY SYNDROME" done towards fulfillment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch–II) (Cardiology) exams to be conducted in July/August 2009, is a bonafide work of the candidate Dr. Leena Thomas, Senior Post graduate student in the Department of Cardiology, Christian Medical College, Vellore under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

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TITLE OF THE STUDY

A prospective, single arm, open trial to assess the safety and efficacy of fondaparinux in unstable angina and non-ST elevation myocardial infarction compared to historical controls treated with enoxaparin.

CONTENTS

ABSTRACT

Background: The OASIS-5 trial demonstrated that fondaparinux was noninferior to enoxaparin while reducing the risk of bleeding by 50%. The objective of our study was to assess the effects of fondaparinux in patients with unstable angina or NSTEMI compared to historical controls treated with enoxaparin. This study is designed to assess the utility of fondaparinux in our current clinical practice.

Methods: We prospectively included 40 patients with unstable angina or NSTEMI to receive fondaparinux (2.5 mg daily) for a mean duration of 5 days and evaluated the composite of death, myocardial infarction, or refractory ischemia at 30 days as the primary efficacy outcome and major bleeding or stroke at 1 month as the primary safety outcome. Historical controls included 44 patients treated with enoxaparin 1mg/kg twice daily.

Results: The effect of fondaparinux versus enoxaparin on the primary composite outcome of death, myocardial infarction, and refractory ischemia at 30 days was similar (27.5% versus 34% p=0.51). The differences in rates of death or refractory ischemia at 30 days between the 2 groups were also not statistically significant (5% versus 6.8%, p=0.72 and 22.5% versus 27.2%, p=0.61). There was no documented myocardial infarction, major or minor bleeding or stroke during the study period. There was a non-significant trend toward a lower 1 week mortality in the fondaparinux group (0% vs. 6.8%, P=0.09). The rate of revascularization procedures at 1 month was similar between the 2 groups. When compared to OASIS 5 trial, patients in our study had more frequent hospitalizations for refractory ischemia but less revascularization procedures.

Conclusion: In this study fondaparinux was found not superior to enoxaparin in the treatment of unstable angina/NSTEMI when primary composite outcome measures are compared at 1 month. Expected reduction in major/minor bleeding and stroke with fondaparinux was not found in this trial. This is likely to be due to small number of patients and low rates of revascularization procedures.

INTRODUCTION

Unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) constitutes a clinical syndrome subset of acute coronary syndrome (ACS) that is usually, but not always, caused by atherosclerotic coronary artery disease (CAD) and is associated with an increased risk of cardiac death and subsequent myocardial infarction. In the spectrum of acute coronary syndrome, UA/NSTEMI is defined by ECG ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent) [1].

UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity, that is, whether the ischemia is severe enough to cause myocardial injury with the release of a marker of myocardial injury. The appearance of these biomarkers may be delayed by up to several hours after the onset of ischemic symptoms, after which the differentiation between UA and NSTEMI (i.e., elevated biomarkers) can be made definitively.[2]

Anticoagulant therapy is essential to modify the ACS disease process and its adverse consequences. A combination of aspirin, an anticoagulant, and additional antiplatelet therapy represents the most effective therapy.[3,4] The intensity of treatment is tailored to individual risk, and triple-anticoagulant treatment is used in patients with continuing ischemia or with other high-risk features and in patients oriented to an early invasive strategy.[1]

An increasing number of anticoagulants (previously referred to as antithrombins) have become available for management of patients with UA/NSTEMI. Although each agent or regimen reviewed (un-fractionated heparin[UFH] , enoxaparin, fondaparinux, and bivalirudin [invasive strategy only]) satisfies criteria for effectiveness, it is often difficult to conclude that one antithrombotic strategy is preferred over another, given differing study designs (blinded vs. unblinded; superiority vs. noninferiority) and questions of equipotent dosing; differing patient populations (higher vs. lower risk), durations of therapy, and strategies (invasive vs. conservative); confounding by open-label and crossover use of anticoagulants; differing antiplatelet strategies; and differing study protocols.[1]

Unfractionated heparin accelerates the action of circulating antithrombin, which inactivates factor IIa (thrombin), factor IXa, and factor Xa. Unfractionated heparin prevents thrombus propagation and prevents early ischemic events. Most of the benefit is short term, with reactivation of the thrombotic process ("rebound") after the discontinuation of UFH contributing to the loss of early gain.[5]

Low-molecular weight heparin(LMWHs) have been widely tested as a means of improving on anticoagulation with UFH. These agents combine factor IIa and factor Xa inhibition and thus inhibit both the action and generation of thrombin. Advantages of LMWH over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance, with a longer half-life. This results in more predictable and sustained anticoagulation with once- or twice-a-day subcutaneous administration that usually does not require laboratory monitoring.[6]

Unstable angina/NSTEMI trials of LMWH and ASA compared with ASA alone or with UFH have generally shown favorable results. The incremental benefit of enoxaparin over UFH shown in certain trials appeared to be driven largely by a reduction in nonfatal MI. [7]

The contemporary practice of using double anti-platelet agents, an anti-thrombotic agent and an invasive strategy have substantially reduced ischemic events, but increased the rate of bleeding. Given that major bleeding has serious long-term consequences, treatment strategies that reduce the risk of bleeding while maintaining or enhancing the benefits of reduced ischemic events are required. Fondaparinux is an important step toward such strategy.[8]

Fondaparinux, a synthetic pentasaccharide, selectively binds antithrombin III and causes rapid and predictable inhibition of factor Xa. Previous studies (OASIS 5) showed that fondaparinux and enoxaparin have similar short term efficacy, fondaparinux substantially reduces bleeding and the reduced bleeding and that accompanies the use of fondaparinux is associated with lower long-term mortality and morbidity. In addition there were significantly fewer strokes with fondaparinux than with enoxaparin.[8]

AIM AND OBJECTIVE

AIM:

The aim of the study is to assess the safety and efficacy of fondaparinux in patients with unstable angina and myocardial infarction without ST elevation.

OBJECTIVE:

The objective of our study was to assess the effects of fondaparinux in patients with unstable angina or non-ST elevation myocardial infarction compared to historical controls treated with enoxaparin.

REVIEW OF LITERATURE

Each year about 1.3million patients have unstable angina or non-ST elevation myocardial infarction, a condition also referred to as non-ST elevation acute coronary syndrome (NSTE-ACS).[9] Acute total occlusion of a coronary artery usually causes ST elevation myocardial infarction (STEMI), whereas UA/NSTEMI usually results from severe obstruction, but not total occlusion of the culprit coronary artery. These potentially life-threatening disorders are a major cause of emergency medical care and hospitalization in developed and developing world.

Definition and classification

Unstable angina is defined as angina pectoris or equivalent type of ischemic discomfort which occurs at rest or with minimal exertion, with at least one of 3 features 1) usually lasting more than 20 minutes, 2) being severe and described as frank pain and of new onset (i.e., within 1 month) and 3) occurring with a crescendo pattern (i.e., more severe, prolonged, or frequent than previously).[2] Of this group, approximately one half will have evidence of myocardial necrosis on the basis of elevated cardiac serum markers, and thus have a diagnosis of NSTEMI.

A clinical classification of UA/NSTEMI by Braunwald has been found to be useful in risk stratification.[10]

TABLE 53–1	Braunwald Clinical Classification of UA/NSTEMI	
Class	**Definition**	**Death or MI to One Year* (%)**
Severity		
Class I:	New onset of severe angina or accelerated angina; no rest pain	7.3
Class II:	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	10.3
Class III:	Angina at rest within 48 hr (angina at rest, subacute)	10.8†
Clinical Circumstances		
A. (Secondary Angina)	Develops in the presence of extracardiac condition that intensifies myocardial ischemia	14.1
B. (Primary Angina):	Develops in the absence of extracardiac condition	8.5
C. (Post Infarction Angina):	Develops within 2 wk after acute myocardial infarction	18.5‡
Intensity of treatment	Patients with unstable angina may also be divided into three groups depending on whether unstable angina occurs (1) in the absence of treatment for chronic stable angina; (2) during treatment for chronic stable angina; or (3) despite maximal antiischemic drug therapy. There three groups that may be designated subscripts 1, 2, and 3, respectively.	
ECG changes	Patients with unstable angina may be further divided into those with or without transient ST-T wave changes during pain.	

*Data from TIMI III Registry: Scirica BM, et al: Am J Cardiol 90:821-826, 2002.
†$p = 0.057$
‡$p < 0.001$.
UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction.
From Braunwald E: Unstable angina: A classification. Circulation 80:410-4, 1989.

(From Braunwald E: Unstable angina: A classification. Circulation 80:410-4, 1989.)

Patients fall into 3 groups

1. primary unstable angina
2. Secondary angina (angina related to precipitating factors such as anemia)
3. Post-MI unstable angina

Patients are also classified according to the severity of the ischemia.

This classification predicts coronary thrombus at angiography, as well as prognosis.

PATHOPHYSIOLOGY

Five pathophysiological processes may contribute to the development of UA/NSTEMI. [11] The acute event usually involves thrombus formation at the site of a ruptured or eroded atherosclerotic plaque, is currently referred to as atherothrombosis, a term that that is replacing atherosclerosis.

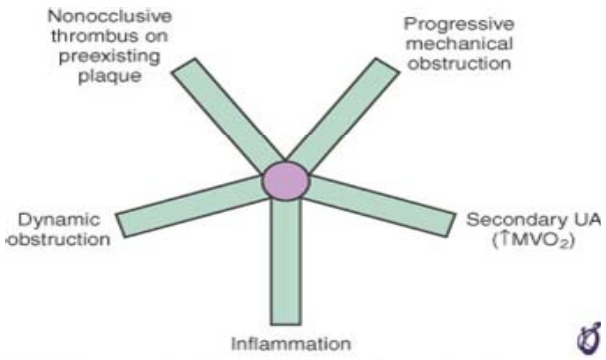


FIGURE 53–1 Schematic representation of the causes of unstable angina (UA). MVO_2 = myocardial O_2 consumption.

(Reproduced from Braunwald E: Unstable angina: An etiologic approach to management. Circulation 98:2219-22, 1998.)

1. Plaque rupture or erosion with superimposed non-occlusive thrombus – the most common cause
2. Dynamic obstruction – coronary spasm as in Prinzmetal angina
3. Progressive mechanical obstruction
4. Inflammation
5. Secondary unstable angina due to increased demand or decreased supply (anemia).

A sequence of events has been documented in UA/NSTEMI, in which there is first a reduction in coronary sinus oxygen saturation (signifying a reduction in coronary blood flow), then ST segment depression, followed by chest discomfort, and elevation in blood pressure or heart rate.[15]

Presentations of UA and NSTEMI

Women present more often with unstable angina, comprising 30 to 45% of patients with unstable angina compared with 25 to 30% of patients with NSTEMI and 20% of the patients with STEMI. In comparison to patients with STEMI, patients with unstable angina have higher rates of prior MI, angina, previous coronary revascularization and extra-cardiac vascular disease. Indeed, approximately 80% of patients with UA/NSTEMI have a history of cardiovascular disease and most have evidence of prior coronary risk facors.[16]

Angina is graded according to the Canadian Cardiovascular Society classification.[12]
Non–ST-elevation MI generally presents as prolonged, more intense rest angina or angina equivalent.

The 5 most important factors on the initial history, in order of importance, are

1) Nature of the anginal symptoms

2) Prior history of CAD

3) Sex (male)

4) Older age

5) An increasing number of traditional risk factors.[13,14]

In patients without preexisting clinical CAD, older age is the most important factor.

Patients with UA/NSTEMI may have discomfort typical of chronic angina except that the episodes are more severe, are prolonged, occur at rest, or are precipitated by less exertion.

Many people are unaware that symptoms besides chest discomfort, such as shortness of breath, diaphoresis, or extreme fatigue, can represent anginal equivalents.[18]

The average UA/NSTEMI patient does not seek medical care for approximately 2 hours after symptom onset**.**[17] Reasons for this delay have been studied and include a mismatch between expectation and actual symptoms and an impression that symptoms are self-limited or are due to other chronic conditions**.**[19,20]

As many as one half of all Acute Myocardial Infarctions (AMI) are clinically silent or unrecognized, and one third present with symptoms other than chest discomfort**.** Patients without chest discomfort are more likely to be older, to be women, to have diabetes mellitus, to have prior HF, and to delay going to the hospital. They also are less likely to be diagnosed correctly initially and to receive appropriate therapies. [21]

Clinical examination

The physical examination may be unremarkable or may support the diagnosis of ischemia. Signs that suggest that UA/STEMI involves a large fraction of the LV include diaphoresis, pale cool skin, sinus tachycardia, a third or fourth heart sound, lung basilar rales and hypotension.[1]

ECG

In UA/NSTEMI, ST depression or transient ST elevation and T wave changes occur in up to 50% of patients. ST deviation is a specific and important measure of ischemia and prognosis. Traditionally, ST segment depression has only been considered significant if it is more than or equal to 0.1mv as occurs in 20 to 25% of patients. An additional 20% of patients will present with 0.05 mv ST depression and they can have an adverse prognosis approaching that of patients with 0.1mv ST depression. Transient (<20 min) ST segment elevation which occurs in approximately 10% of patients, portends the worst prognosis in UA/NSTEMI. T wave changes are sensitive but not specific for acute ischemia, unless they are marked (>0.3 mv).[1]

Early risk stratification

Patients who present with chest discomfort should undergo early risk stratification for the risk of cardiovascular events (e.g., death or [re]myocardial infarction).[1]

If the initial ECG is not diagnostic but the patient remains symptomatic and there is high clinical suspicion for acute coronary syndrome, serial ECGs, initially at 15- to 30-min intervals, should be performed to detect the potential for development of ST-segment elevation or depression.

Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with acute coronary syndrome. A cardiac-specific troponin is the preferred marker. Patients with negative cardiac biomarkers within 6 h of the onset of symptoms

consistent with acute coronary syndrome should have biomarkers re-measured in the time frame of 8 to 12 h after symptom onset.[22]

Several risk-prediction models exist for patients with acute coronary syndrome, both from randomized clinical trials and from registries.

The Global Registry of Acute Coronary Events (GRACE) prediction model is a robust tool for predicting in hospital and 6-month mortality in patients with all types of acute coronary syndrome.[23] The European Society of Cardiology Guidelines for the diagnosis and treatment of patients with acute coronary syndrome recommend the GRACE risk score as the preferred classification, and the ACC/AHA Guidelines gives the option of using one of three validated risk scores—GRACE, Thrombolysis in Myocardial Infarction (TIMI) or, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), in helping to select medical and interventional therapies.[24,25]

Early risk stratification – ACC/AHA recommendations

Class I

1. A rapid clinical determination of the likelihood risk of obstructive CAD (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an acute coronary syndrome (ACS) and considered in patient management.

2. Patients who present with chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events that focuses on history, physical findings, ECG findings, and biomarkers of cardiac injury and results should be considered in patient management.

CLASS IIa

1. Use of risk-stratification models, such as the Thrombolysis In Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) risk score or the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model can be useful to assist in decision making with regard to treatment options in patients with suspected ACS.

TABLE 53G-1 American College of Cardiology/American Heart Association System for Risk Stratification of Patients with Unstable Angina

Feature	High Risk *At Least One of the Following Features*	Intermediate Risk *No High-Risk Feature but Must Have One of the Following*	Low Risk *No High- or Intermediate-Risk Feature but May Have Any of the Following Features*
History	Accelerating tempo of ischemic symptoms in preceding 48 hr	Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20 min) rest pain	Prolonged rest angina, now resolved, with moderate or high likelihood of CAD Rest angina < 20 min or relieved with rest or sublingual NTG	New-onset or progressive CCS Class III or IV angina the past 2 wk without prolonged rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema, most likely caused by ischemia New or worsening MR murmur S_3 or new worsening rales Hypotension, bradycardia, tachycardia Age > 75 yr	Age > 70 yr	
ECG	Angina at rest with transient ST segment changes > 0.05 mV Bundle branch block, new or presumed new Sustained ventricular tachycardia	T wave inversions > 0.2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated	Slightly elevated	Normal

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; NTG = nitroglycerin.

TABLE 53G–1 American College of Cardiology/American Heart Association System for Risk Stratification of Patients with Unstable Angina.

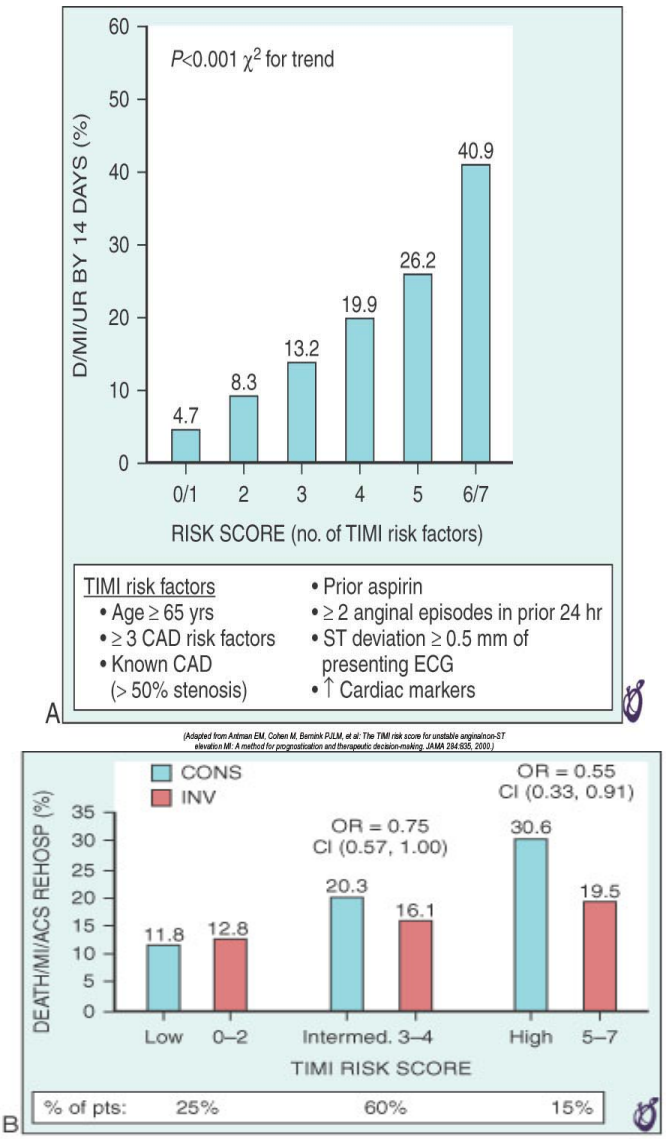


FIGURE 53–8B A, Thrombolysis in myocardial ischemia (TIMI) risk score for unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI). The risk factors are shown below and the risk of death (D), myocardial infarction (MI), or urgent revascularization (UR) is shown along the vertical axis. **B,** Use of the TIMI risk score for UA/NSTEMI to predict the benefit of an early invasive strategy. In a prospectively defined analysis, the TIMI risk score was applied in the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial. As shown, 75 percent of patients had a risk score of 3 or higher, and in these patients a significant benefit of an invasive strategy was observed. ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CONS = conservative; ECG = electrocardiogram; INV = invasive; OR = odds ratio.

(Data from Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879, 2001.)

Table 4. TIMI Risk Score for Unstable Angina/Non–ST-Elevation MI

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %
0–1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6–7	40.9

The TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the following variables: age 65 y or older; at least 3 risk factors for CAD; prior coronary stenosis of 50% or more; ST-segment deviation on ECG presentation; at least 2 anginal events in prior 24 h; use of aspirin in prior 7 d; elevated serum cardiac biomarkers. Prior coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events. Reprinted with permission from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42 (46). Copyright © 2000 American Medical Association.

Use of the TIMI risk score for UA/NSTEMI to predict the benefit of an early invasive strategy. TIMI risk score was applied in TACTICS-TIMI 18 trial. Seventy five percentage of patients had a risk score of 3 or higher, and in these patients a significant benefit of an invasive strategy was observed. [26]

Rationale for the Conservative Strategy

The conservative strategy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. With this strategy, an early echocardiogram should be considered to identify significant LV systolic dysfunction.

In addition, an exercise or pharmacological stress test is recommended before or shortly after discharge to identify patients with latent ischemia who could benefit from revascularization. The use of aggressive anticoagulant and antiplatelet agents has reduced the incidence of adverse outcomes in patients managed conservatively (ACC/AHA).[1]

Rationale for the Invasive Strategy

The routine use of angiography within 24 h of hospital admission provides an invasive approach to risk stratification. It can identify the 10% to 20% of patients with no significant coronary stenosis as well as the approximately 20% with 3-vessel disease with LV dysfunction or left main CAD who derive a substantial survival benefit from CABG. For the other approximately 60% to 70%, PCI of the culprit lesion can reduce subsequent hospitalizations and the need for multiple antianginal drugs. Contemporary anticoagulant and antiplatelet therapies have lessened the early hazard of PCI.

Excluding those in need of urgent intervention, 2 alternatives for the invasive approach have emerged: early ("immediate") or deferred angiography (i.e., before or after a 12- to 48-hours window).

Support for immediate angiography comes from the Intracoronary Stenting with Antithrombotic Regimen Cooling-off Study (ISAR-COOL).[27] In that trial patients randomized to immediate angiography had fewer deaths or MIs at 30 d (5.9% vs. 11.6%, p= 0.04).

Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial randomized patients to routine invasive or selective invasive management. At the end of one year, there was no significant difference in the composite ischemic end point. [28]

RITA-3 trial (Third Randomized Intervention Treatment of Angina) randomized patients to interventional vs conservative treatment[29]. At one year, death and MI rates were similar, but at 5 years, a significant reduction in death or MI emerged in the early invasive treatment arm, mainly in high-risk patients.

Long-term outcomes of the FRagmin and fast revascularization during InStability in Coronary artery disease (FRISC II) trial. [30] At 5 years, the invasive strategy was favored for the primary end point of death or nonfatal MI (HR 0.81, p = 0.009). Benefit was confined to men, nonsmokers, and patients with 2 or more risk factors**.**

A meta-analysis of 7 randomized trials of management strategies in UA/NSTEMI, supports the long-term benefit of an early invasive strategy in terms of all-cause mortality at 2 years, nonfatal MI and rate of hospitalization.[31]

When a patient with high risk ACS is admitted treatment should be initiated and an early invasive strategy should be considered. In an early conservative strategy patients are stabilized with medical therapy and angiography and revascularization is performed if patients have recurrent symptoms or ischemia, heart failure or serious arrhythmias. Patients managed according to early conservative strategy should undergo an assessment of LV function and a stress test; they should also undergo angiography if they are found to

have ejection fraction less than 40% or if they have an intermediate or high risk exercise test result.

TREATMENT OF UNSTABLE ANGINA / NSTEMI

Anticoagulants

Patients with non–ST-elevation ACS are a heterogeneous population with respect to short- and long-term morbidity and mortality. The optimal treatment strategy for these patients continues to evolve, and there is a wide range of therapeutic options.

Anticoagulant therapy is essential to modify the ACS disease process and its adverse consequences. A combination of aspirin, an anticoagulant, and additional antiplatelet therapy represents the most effective therapy. The intensity of treatment is tailored to individual risk. Patients with continuing ischemia or with other high-risk features and should undergo early invasive strategy.

UNFRACTIONATED HEPARIN

Anticoagulation traditionally with Unfractionated heparin (UFH) is a cornerstone of therapy for patients with UA/NSTEMI. UFH is a heterogeneous mixture of polysaccharide chains of molecular weights that range from 5,000 to 30,000 Daltons and that have varying anticoagulant activity.[32] Unfractionated heparin accelerates the action of circulating antithrombin, which inactivates factor IIa (thrombin), factor IXa, and factor Xa. Unfractionated heparin prevents thrombus propagation but does not lyse existing thrombi.

Meta-analysis of a relatively small, randomized database suggests a reduction of 33% to 56% (p=0.06 to 0.03) in early ischemic events by the addition of UFH. But reactivation of the thrombotic process after the discontinuation of UFH contributes to the loss of early gain.[33,34]

Unfractionated heparin binds to a number of plasma proteins, blood cells, and endothelial cells, leading to the poor bioavailability, especially at low doses, and marked variability in anticoagulant response. As a consequence, the anticoagulant effect of heparin requires monitoring with the activated partial thromboplastin time (aPTT). The duration of UFH therapy in most UA/NSTEMI trials has been 2 to 5 days. The optimal duration of therapy is uncertain and likely varies by strategy.

LOW-MOLECULAR-WEIGHT HEPARIN

The low-molecular weight heparins (LMWHs) are obtained through chemical or enzymatic depolymerization of the polysaccharide chains of heparin to provide chains with different molecular-weight distributions. LMWHs are relatively more potent in inhibiting factor Xa than inactivating thrombin.[35]

Advantages of LMWH over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance, with a longer half-life. This results in more predictable and sustained anticoagulation with once- or twice-a-day subcutaneous administration that usually does not require laboratory monitoring. In addition to providing ease of administration and eliminating the need for monitoring, LMWHs stimulate platelets less than UFH and less frequently cause heparin-induced thrombocytopenia.[35]

LMWH (plus aspirin) has proved effective compared with aspirin alone, leading to a 66 percent reduction in the odds of death or MI.[5] Eight randomized trials have directly compared a LMWH with UFH. Trials with dalteparin and nadroparin reported similar rates of death or nonfatal MI compared with UFH, whereas 5 of 6 trials of enoxaparin favored enoxaparin. This benefit of enoxaparin was largely by a reduction in nonfatal MI.

With an early invasive strategy, outcomes with UFH and LMWH (enoxaparin) were similar.[36] Trials which evaluated the potential benefit of prolonged administration of LMWH after hospital discharge, showed little or no benefit beyond the acute phase.[30] LMWH is associated with more frequent minor but not major bleeding. A post hoc analysis from the SYNERGY trial suggested that some of the excess bleeding seen with enoxaparin could be explained by crossover to UFH at the time of PCI.[36]It thus appears reasonable to maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself.

A prospective analysis of the A to Z trial showed that enoxaparin provided significant benefit over UFH in patients managed conservatively but not in those managed invasively.[37]

Two new anticoagulants, fondaparinux and bivalirudin, have undergone favorable testing in clinical trials and are recommended as alternatives to unfractionated heparin and low-molecular-weight heparins for specific or more general applications.

FACTOR XA INHIBITORS

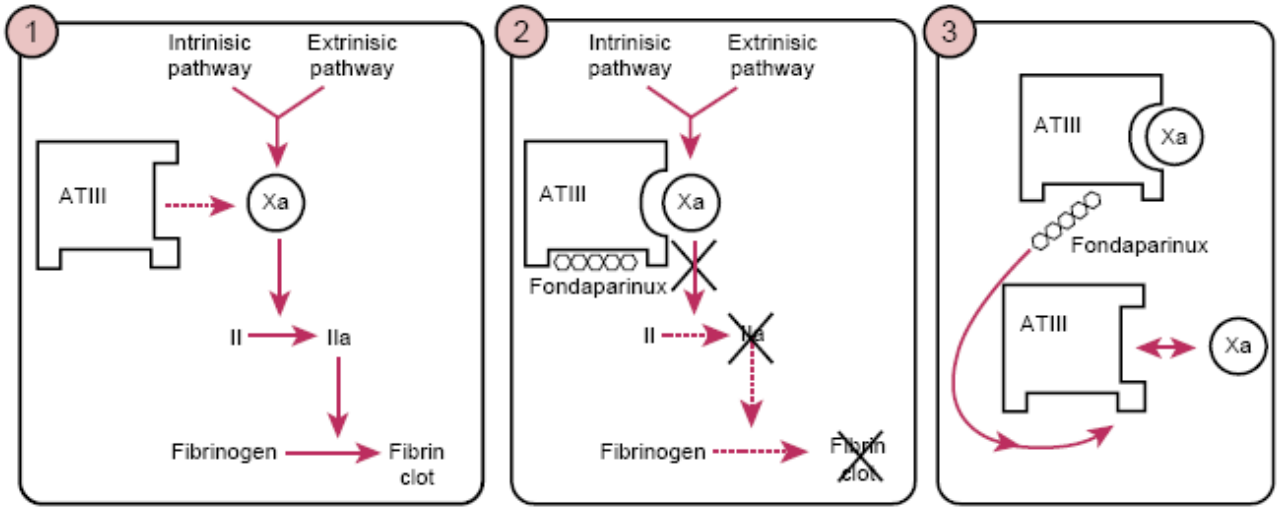
Factor Xa inhibitors act proximally in the coagulation cascade to inhibit the multiplier effects of the downstream reactions, thereby suppressing thrombin generation.[38]

FONDAPARINUX

Fondaparinux sodium is the first of a new class of synthetic antithrombotic drugs. It is the sodium salt of a sulphated pentasaccharide, obtained totally by chemical synthesis.

Mechanism of action

The antithrombotic activity of fondaparinux is the result of antithrombin III (AT III) -mediated selective inhibition of factor xa. By selectively binding to AT III, fondaparinux potentiates about 300 times the the innate neutralization of factor xa by AT III.[39] Neutralization of factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.



Mechanism of action of fondaparinux. Figure (1) The activation of the coagulation cascade results in the formation of thrombin and a fibrin clot. The inhibition of Factor Xa by antithrombin (ATIII) is very slow. (2) Fondaparinux binds specifically to ATIII. ATIII undergoes a conformational change after binding to fondaparinux. Bound to fondaparinux, ATIII inhibits Factor Xa selectively and rapidly. By inhibiting Factor Xa, thrombin generation and fibrin formation are blocked. (3) Fondaparinux is released to act on other molecules of ATIII.

Fondaparinux also inhibits clot-bound Factor Xa, but not Factor Xa within the prothrombinase complex. When released from ATIII, fondaparinux can exert its action again; each molecule of fondaparinux mediates the inhibition of several molecules of Factor Xa. The highest therapeutic doses of fondaparinux (which result in fondaparinux plasma concentrations up to 1.2 μm at 10 mg once daily) do not saturate plasma ATIII, the plasma concentration of which is 2–3 μm. By increasing the ability of ATIII to inhibit Factor Xa, a factor situated at the junction of the intrinsic and extrinsic pathways of the coagulation cascade, fondaparinux efficiently inhibits thrombin generation. Its synthetic nature eliminates the theoretical risk of pathogen contamination and assures batch-to-batch consistency. [39]

PHARMACODYNAMICS

The effect of therapeutic doses of fondaparinux on routine laboratory hemostasis tests, including activated partial thromboplastin time, prothrombin time, activated clotting time and bleeding time, is very limited.[40,41] When necessary, fondaparinux may be

assayed in plasma using a specific anti-Factor-Xa chromogenic method. [42]

Fondaparinux did not exhibit cross-reactivity with heparin-induced thrombocytopenia (HIT) sera, did not bind to platelet factor4, did not influence lipid metabolism and did not alter central nervous system, cardiovascular, respiratory, renal or gastrointestinal function.

Preclinical data reveal no special risk for human based on conventional studies of safety pharmacology, repeated dose toxicity (up to 3 months) and genotoxicity (in vitro and in vivo). [39]

Pharmacokinetics

Fondaparinux administered by subcutaneous injection is rapidly and completely absorbed. In contrast to the heparins, fondaparinux selectively binds to antithrombin and causes rapid and predictable inhibition of factor Xa.[38]. Fondaparinux has a bioavailability via subcutaneous injection of 100% and reaches half maximum plasma concentration within 25 minutes with a half-life of 15 hours.

It has linear pharmacokinetics and low inter- and intra-individual variability, thus obviating the need for laboratory monitoring and enabling a once-daily dosing scheme. After once daily dosing, steady state of plasma levels is obtained after 3 to 4 days. Distribution volume is limited and consistent with blood volume. Fondaparinux is highly and specifically bound to AT III in plasma. There is no evidence of biotransformation.

Fondaparinux is renally cleared and reduced plasma clearance is observed in patients with renal insufficiency. It is eliminated in urine mainly as unchanged drug. The elimination half-life is 17-21 hrs in healthy subjects. [43]

Fondaparinux does not inhibit cytochrome p450 isoenzymes. In clinical studies performed with fondaparinux, the concomitant use of oral anticoagulants, antiplatelets, non-steroidal anti-inflammatory drugs, and digoxin did not affect the pharmacokinetics of fondaparinux.[41] In addition, fondaparinux neither influenced the pharmacodynamics of warfarin, acetyl salicylic acid and digoxin, nor the pharmacokinetics of digoxin at steady state.

At high doses used in safety studies, adequate exposure was confirmed. This exposure increase with dose, but with evidence of non-linear pharmacokinetics due to saturable protein binding (AT III).The factor Xa inhibitors do not have any action against thrombin that is already formed, a possible explanation for the increased rate of catheter associated thrombosis with fondaparinux. [43]

Advantages of the pentasaccharide factor Xa inhibitor fondaparinux over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance with a longer half-life, which results in more predictable and sustained anticoagulation and allows fixed-dose, once-daily subcutaneous administration.
As with the LMWHs, fondaparinux does not require laboratory monitoring.

Table 1. Main pharmacological properties of fondaparinux.

	Fondaparinux
Source	Synthetic
Structure	Homogeneous
Target	Single (Factor Xa)
Protein binding in plasma	Antithrombin only
Administration	Once daily, subcutaneously
Bioavailibility	100%
Time to peak plasma concentration (Tmax)	2 hours
Time to plasma concentration of Cmax/2	25 minutes
Half-life	17 hours
Pharmacokinetic profile	Linear, dose-independent
Hepatic metabolism	No
Elimination	Unchanged in urine
Monitoring of coagulation parameters	No
Drug interactions	None known
Cross-reactivity with antibodies involved in heparin-induced thrombocytopenia	No

It is available in the form of disposable pre-filled syringes. The solution is sterile, endotoxin free, isotonic and suitable for IV or subcutaneous injection.

Clinical trials with fondaparinux

Studies in healthy volunteers

Safety and pharmacokinetics of fondaparinux was assessed in 21 phase I studies in healthy male and female, young and elderly subjects. Moreover a study was performed in patients with renal impairment.

Pharmacodynamic data in human with fondaparinux are in agreement with a selective inhibition of factor Xa. No significant changes have been observed for the primary hemostasis parameters. According to a study in healthy volunteers, recombinant factor VIIa is capable of normalizing coagulation times and thrombin generation during fondaparinux treatment. Recombinant factor VIIa may be useful to reverse the anticoagulant effect of fondaparinux in case of serious bleeding complications or need for emergency surgery during treatment with fondaparinux. [43]

Study in patients

Prevention of venous thromboembolism

A study evaluated the response of fondaparinux in prevention of venous thromboembolism in patients undergoing major orthopaedic surgery.

Four phase III studies to demonstrate the superior efficacy of fondaparinux 2.5 mg once daily SC over enoxaparin in preventing venous thromboembolism – Ephesus study, Pentathalon, Pentamarks and Penthifra.[44] Evaluation of pooled data revealed an overall odds reduction of 56% for efficacy compared to enoxaparin. Hence the overall result demonstrated fondaparinux to be superior to enoxaparin for efficacy. Overall major and minor bleeding rates were similar between fondaparinux 2.5mg and LMWH.

Prevention of venous thromboembolism in high risk abdominal surgery

A phase III study named Pegasus to compare the efficacy and safety of fondaparinux 2.5mg given post-operatively with dalteparin concluded that post-operative administration of fondaparinux was at least as effective as safe as dalteparin in patients at high risk for

venous thromboembolism, with a significantly superior control achieved in patients with cancer surgery receiving fondaparinux.[45]

Prevention of venous thromboembolism in acutely ill medical patients

The Artemis study demonstrated that fondaparinux is safe and effective in prevention of venous thromboembolism in acutely ill medical patients at moderate to high risk. [46]

Treatment of venous thromboembolic disease

Rembrandt study – a multi-centre, randomized, double-blind dose ranging study performed in patients with symptomatic proximal deep vein thrombosis (DVT). Fondaparinux was compared with dalteparin. Fondaparinux appears to be an effective and safe treatment for patients with DVT across a wide range of doses (5.0, 7.5, 10.0 mg OD SC).[47]

The MATISSE- DVT study and MATISSE- PE study showed that once daily subcutaneous fondaparinux was at least as effective and equally safe as the reference therapy (bid body weight-adjusted enoxaprin in DVT and aptt adjusted UFH in pulmonary embolism) in the initial treatment of symptomatic venous thromboembolism. [48,49]

Thus it is proved that Fondaparinux is more effective than enoxaparin in preventing venous thrombosis in patients undergoing orthopedic surgery and is similar in effectiveness to enoxaparin or UFH in patients with deep-vein thrombosis or pulmonary embolism.

FONDAPARINUX IN ACUTE CORONARY SYNDROME

In the PENTALYSE dose ranging study, it was hypothesized that prolonged factor Xa inhibition with fondaparinux may be an effective and safe antithrombotic co-therapy to thrombolysis in acute myocardial infarction. [50] Patients with STEMI were treated with alteplase and randomized to UHF, given intravenous (IV) for up to 72hrs or to fondaparinux. Fondaparinux was given in 3 different doses – 4mg, 8mg, and 12mg, administered daily for 5 to 7 days, IV on the first day, then subcutaneously. TIMI grade 3 flow rates at 90 min were similar in all groups. Moreover, a strong trend towards less re-occlusion of the infarct-related vessel at day 5 to 7 was observed with fondaparinux. Also fewer revascularization during the 30-day follow-up period were performed in patients given fondaparinux. The primary safety endpoint, the combined incidence of intracranial haemorrhage and need for blood transfusion, was identical for fondaparinux and UFH.

A dose ranging PENTUA study in patients with UA/ NSTEMI was performed testing four fondaparinux dose levels (2.5, 4.0, 8.0 and 12.0). [51] This was a double blind, randomized controlled study testing four fondaparinux doses and a body weight adjusted dose regimen of enoxaparin (1 mg/kg bid). The objectives were to assess the dose response relationship of fondaparinux for the primary efficacy endpoint - the composite of death, AMI, recurrent ischemia and to select the optimum dose levels for treating patients with non-ST elevation ACS. All fondaparinux dose levels tested appeared to be efficacious and at least as effective as enoxaparin (1 mg/kg bid). With respect to safety, all doses of fondaparinux appeared to be as safe as enoxaparin and also no dose-related safety profile was noted. However, it was noticed that in the fondaparinux 2.5mg dose group, the incidence of death,

MI and recurrent ischemia was significantly lower than in the enoxaparin group and no major bleeding was observed. Consequently, the lowest dose of fondaparinux (2.5mg) has been selected for further clinical studies in acute coronary syndromes.

A Pilot trial (ASPIRE) involving patients with acute coronary syndromes undergoing percutaneous coronary intervention suggest that fondaparinux may be as effective as enoxaparin or safer than unfractionated heparin.[52]

There are several reasons why fondaparinux might be used instead of enoxaparin in UA and NSTEMI. [62] First, the use of multiple antithrombotic therapies and the performance of acute interventions routinely in ACS have led to higher rates of major bleeding. New anticoagulants must therefore demonstrate either reduced bleeding complications without compromising efficacy or alternatively significantly reduce major efficacy events to a clinically important degree that would make any additional bleeding risk acceptable. The ideal scenario would be if the new anticoagulant improved efficacy and reduced bleeding.

In the trials of prevention of venous thrombosis, fondaparinux was clearly associated with improved efficacy over enoxaparin, with no significant increase (and in some trials a reduction) in major bleeding, particularly when the 2.5-mg dose was used.

Second, fondaparinux is simpler to administer because it is given once daily versus a twice daily enoxaparin regimen.

Third, fondaparinux is a synthetic compound, and thus there is no chance of animal to human transmission of infectious agents. By contrast, enoxaparin is harvested from porcine intestines, introducing the potential for animal to human transmission. Although this has not been a major concern to date, it remains a theoretical possibility with potentially important consequences for treatment of human subjects.

Table 2. Clinical trials on fondaparinux.

Indication	Phase	Study	Fondaparinux	Comparator	Duration of therapy	No. of patients enrolled
Prevention of venous thromboembolism in elective hip replacement surgery	II	PENTATHLON	0.75, 1.5, 3, 6 and 8 mg once daily starting postoperatively	Enoxaparin, 30 mg twice daily starting postoperatively[a]	5–9 days	933
Prevention of venous thromboembolism in elective hip replacement surgery	III	EPHESUS	2.5 mg once daily starting postoperatively	Enoxaparin, 40 mg once daily starting preoperatively[b]	5–9 days	2309
Prevention of venous thromboembolism in elective hip replacement surgery	III	PENTATHLON 2000	2.5 mg once daily starting postoperatively	Enoxaparin, 30 mg twice daily starting postoperatively[a]	5–9 days	2275
Prevention of venous thromboembolism in hip fracture surgery	III	PENTHIFRA	2.5 mg once daily starting postoperatively	Enoxaparin, 40 mg once daily starting preoperatively[b]	5–9 days	1711
Prevention of venous thromboembolism in elective knee replacement surgery	III	PENTAMAKS	2.5 mg once daily starting postoperatively	Enoxaparin, 30 mg twice daily starting postoperatively[a]	5–9 days	1049
Prevention of venous thromboembolism in hip fracture surgery	III	PENTHIFRA-PLUS	2.5 mg once daily	Placebo once daily	21 ± 1 days after 7 ± 1 days of fondaparinux in both groups	656
Prevention of venous thromboembolism in abdominal surgery in patients aged over 60 years, or over 40 years with obesity, a history of venous thromboembolism, congestive heart failure, chronic obstructive pulmonary disease, inflammatory bowel disease, or surgery for cancer	III	PEGASUS	2.5 mg once daily starting postoperatively	Dalteparin 2500 IU 2 h pre-operatively, then post-operatively on the evening of the day of surgery (212 h after the pre-operative injection) and 5000 IU once daily	5–9 days	2927

(*continued on next page*)

Table 2 (*continued*)

Indication	Phase	Study	Fondaparinux	Comparator	Duration of therapy	No. of patients enrolled
Prevention of venous thromboembolism in acutely ill medical patients aged 60 years or more and expected to undergo bed rest for at least four days for congestive heart failure and/or acute respiratory illness in the presence of chronic lung disease, and/or acute infection or inflammatory disease	III	ARTEMIS	2.5 mg once daily starting postoperatively	Placebo once daily	6–14 days	849
Treatment of venous thromboembolism	II	REMBRANDT	5, 7.5 and 10 mg once daily	Dalteparin, 100 IU/kg twice daily	At least 5 days	453
Treatment of deep vein thrombosis	III	MATISSE-DVT	7.5 mg once daily (5.0 mg in patients < 50 kg, and 10.0 mg in patients > 100 kg)	Enoxaparin 1 mg/kg twice daily	At least 5 days	2200
Treatment of symptomatic pulmonary embolism with or without deep vein thrombosis	III	MATISSE-PE	7.5 mg once daily (5.0 mg in patients < 50 kg, and 10.0 mg in patients > 100 kg)	Adjusted-dose continuous intravenous unfractionated heparin	At least 5 days	2213
Unstable angina or non-Q-wave myocardial infarction	II	PENTUA	2.5, 4, 8 and 12 mg once daily	Enoxaparin 1 mg/kg twice daily	2–8 days	929
ST-segment-elevation acute myocardial infarction	II	PENTALYSE	4, 8 and 12 mg once daily	Unfractionated heparin intravenously 5000 U followed by 1000 U/h	Fondaparinux: 5–7 days Heparin: 2–3 days	333

[a] North-American approved regimen.
[b] Regimen approved worldwide.

Idraparinux

A synthetic long acting analogue of fondaparinux with a prolonged half-life and 10-fold higher binding to factor X that can be given in fixed weekly doses. However, a large trial comparing Idraparinux and vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation was stopped pre-maturely because of excess bleeding. [53]

OASIS-5

The Organization to Assess Strategies for Ischaemic Syndromes (OASIS)-5 investigators evaluated the use of fondaparinux in 20,078 patients with UA/NSTEMI. [8] Patients were randomized (double-blind, double-dummy design) to a control strategy of enoxaparin 1.0 mg/ kg subcutaneous twice daily (reduced to 1.0 mg/ kg once daily for patients with an estimated creatinine clearance < 30 ml / min) or to fondaparinux 2.5 mg subcutaneously, once daily. Unfractionated heparin initially was not used with PCI, but because of an increased incidence of catheter associated thrombus, the protocol was amended to permit the use of open-label UFH at the investigator's discretion.

The OASIS-5 primary composite outcome (death, MI, or refractory ischemia at 9 d) was similar in the 2 groups (579 with fondaparinux [5.8%] vs. 573 with enoxaparin [5.7%]; hazard ratio [HR] 1.01; 95% CI 0.90 to 1.13), which satisfied pre-specified non-inferiority criteria.

Rates of major bleeding at 9 d were lower with fondaparinux (2.2% vs. 4.1%, *p* less than 0.001), which yielded a lower efficacy plus safety composite. This difference persisted during long-term follow-up. Fondaparinux was associated with a significant reduction in rates of major (hazard ratio, 0.55; 95 % confidence interval, 0.41 to 0.74; P<0.001) as well

as minor bleeding (1.1% in the fondaparinux group vs. 3.2% in the enoxaparin group. Fondaparinux significantly reduced the rate of death, as well as the rate of the composite of death, myocardial infarction, and stroke at 30 days. Fondaparinux was associated with substantially less bleeding — an effect that translated into lower long-term mortality and morbidity.

Table 2. Main Efficacy and Safety Outcomes.*

Time and Outcome	Enoxaparin (N=10,021)	Fondaparinux (N=10,057)	Hazard Ratio (95% CI)	P Value for Superiority	P Value for Noninferiority
	no. of events (% of patients)				
9 Days					
Death, MI, or refractory ischemia	573 (5.7)	579 (5.8)	1.01 (0.90–1.13)	NA	0.007
Death or MI†	412 (4.1)	409 (4.1)	0.99 (0.86–1.13)	NA	0.005
Death	186 (1.9)	177 (1.8)	0.95 (0.77–1.17)	NA	
MI	264 (2.7)	263 (2.6)	0.99 (0.84–1.18)	NA	
Refractory ischemia	188 (1.9)	194 (1.9)	1.03 (0.84–1.26)	NA	
Stroke	45 (0.5)	37 (0.4)	0.82 (0.53–1.27)	NA	
Major bleeding	412 (4.1)	217 (2.2)	0.52 (0.44–0.61)	<0.001	
Death, MI, refractory ischemia, or major bleeding	905 (9.0)	737 (7.3)	0.81 (0.73–0.89)	<0.001	
Death, MI, or stroke	446 (4.5)	435 (4.3)	0.97 (0.85–1.11)	0.67	
30 Days					
Death, MI, or refractory ischemia	864 (8.6)	805 (8.0)	0.93 (0.84–1.02)	0.13	
Death or MI	682 (6.8)	619 (6.2)	0.90 (0.81–1.01)	0.07	
Death	352 (3.5)	295 (2.9)	0.83 (0.71–0.97)	0.02	
MI	411 (4.1)	387 (3.9)	0.94 (0.82–1.08)		
Refractory ischemia	222 (2.2)	220 (2.2)	0.99 (0.82–1.19)		
Stroke	95 (1.0)	74 (0.7)	0.77 (0.57–1.05)		
Major bleeding	494 (5.0)	313 (3.1)	0.62 (0.54–0.72)	<0.001	
Death, MI, refractory ischemia, or major bleeding	1238 (12.4)	1025 (10.2)	0.82 (0.75–0.89)	<0.001	
Death, MI, or stroke	752 (7.5)	671 (6.7)	0.89 (0.80–0.98)	0.02	
180 Days					
Death, MI, or refractory ischemia	1308 (13.2)	1222 (12.3)	0.93 (0.86–1.00)	0.06	
Death or MI	1127 (11.4)	1042 (10.5)	0.92 (0.84–1.00)	0.05	
Death	638 (6.5)	574 (5.8)	0.89 (0.80–1.00)	0.05	
MI	635 (6.6)	606 (6.3)	0.95 (0.85–1.06)		
Refractory ischemia	238 (2.4)	231 (2.3)	0.97 (0.81–1.16)		
Stroke	161 (1.7)	127 (1.3)	0.78 (0.62–0.99)	0.04	
Major bleeding	569 (5.8)	417 (4.3)	0.72 (0.64–0.82)	<0.001	
Death, MI, refractory ischemia, or major bleeding	1698 (17.1)	1493 (15.0)	0.86 (0.81–0.93)	<0.001	
Death, MI, or stroke	1234 (12.5)	1113 (11.3)	0.89 (0.82–0.97)	0.007	

* Strokes were prospectively documented and centrally adjudicated. The composite of death, myocardial infarction (MI), or stroke was not a prespecified outcome. CI denotes confidence interval, and NA not applicable.
† The noninferiority criterion was based on the primary outcome, but the secondary outcome of death or MI also satisfied this criterion.

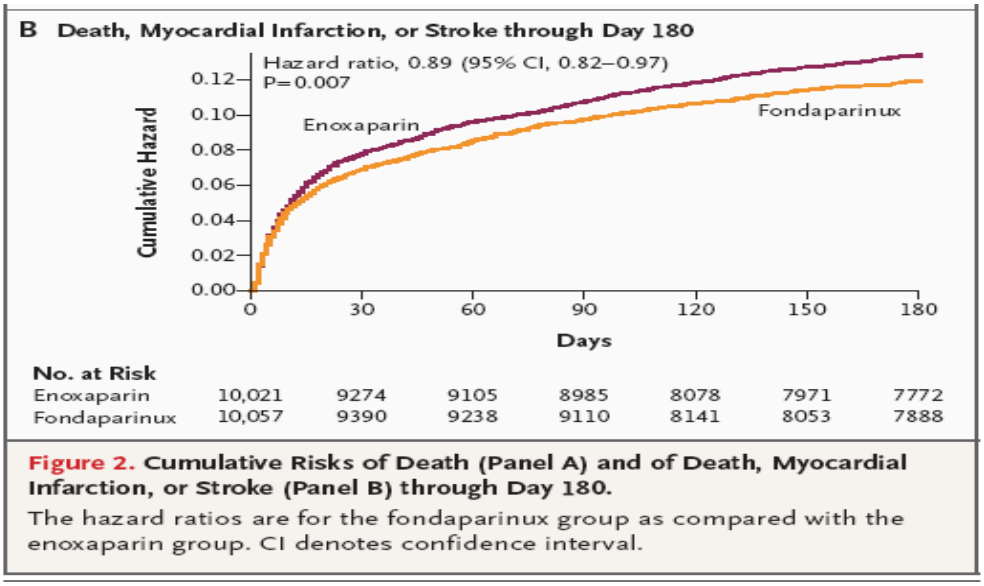
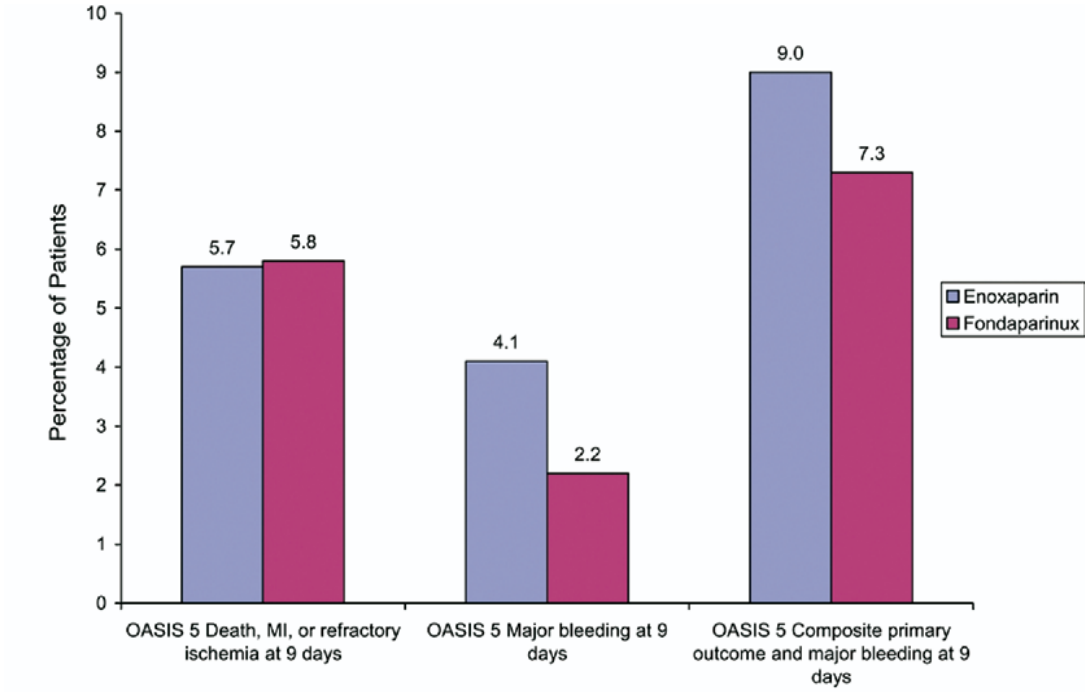


Figure 2. Cumulative Risks of Death (Panel A) and of Death, Myocardial Infarction, or Stroke (Panel B) through Day 180.

The hazard ratios are for the fondaparinux group as compared with the enoxaparin group. CI denotes confidence interval.



OASIS 5 (424)

Absolute Risk Reduction	-0.1	1.9	1.7
Hazard Ratio	1.01	0.52	0.81
95% CI	0.90 to 1.13	0.44 to 0.61	0.73 to 0.89
p	0.007*	less than 0.001†	less than 0.001†

Primary composite events trended lower in the fondaparinux group at 30 d and 6 months; 6-month rates of death (5.8% vs. 6.5%) and death, MI, and stroke (11.3% vs. 12.5%) were also lower at 6 months with fondaparinux.

Three important findings of the OASIS 5 trial

1)lin the short term, fondaparinux and enoxaparin have similar efficacy.

2) As compared with enoxaparin, fondaparinux substantially reduces bleeding.

3) The reduced bleeding that accompanies the use of fondaparinux is associated with lower long-term mortality and morbidity.

Although the rate of death and MI and severe bleeds did not differ significantly between the two groups in patients undergoing PCI, there was a higher rate of guiding catheter thrombosis and more coronary complications (new angiographic thrombus, catheter thrombus or no reflow) with fondaparinux. But addition of UFH with fondaparinux during PCI largely avoided these complications. Given the very limited time for antithrombotic therapy prior to the procedure and the need for UFH during the procedure, there is probably little advantage in using fondaparinux as the initial treatment in patients in whom primary PCI is intended. In all other patients initial management with fondaparinux followed by standard UFH during PCI is an attractive choice.

Fondaparinux appears to represent a preferred anticoagulant strategy in those at higher risk of bleeding managed with a noninvasive strategy.

Noting that fondaparinux can be used as a single fixed dose - the simplicity of the regimen, lack of monitoring, and its safety and efficacy in the full spectrum of acute coronary syndrome facilitates the use of fondaparinux in a range of settings. It may even be applicable in the pre-hospital or post-hospital settings in appropriate patients. The use of aggressive anticoagulant and antiplatelet agents has reduced the incidence of adverse outcomes in patients managed conservatively.

Clinical trials data continue to build support for an initial invasive strategy for higher-risk UA/NSTEMI patients (as assessed by troponin positivity or a formal risk score); in contrast, such a strategy is not of benefit in low-risk patients especially women, in whom an initially conservative strategy is recommended.[31]

fondaparinux will be more preferred in settings in which the use of angiographic-based reperfusion is not routine.

OASIS 6

OASIS-6 trial evaluated the impact of fondaparinux compared with standard approaches to antithrombotic therapy in a broad range of patients with STEMI in preventing the primary and composite outcome of death or reinfarction at 30 days.[54] The trial demonstrated a moderate reduction in mortality and reinfarction with the use of fondaparinux compared with usual care and this benefit persists long term. There was a higher rate of guiding catheter thrombosis if PCI is performed without UFH, but this is largely avoided if UFH is used before the procedure.

Although the use of UFH for PCI in fondaparinux-treated patients appears to be safe and effective, a limitation is that the number of patients treated with this approach remains relatively modest.

The net clinical benefit of fondaparinux was observed consistently in those undergoing both an early invasive and a delayed invasive management strategy and was due primarily to a reduction in major bleeding. These benefits were even more marked after the exclusion of patients referred for primary PCI for STEMI, for whom data from the OASIS 6 trial demonstrated no tangible benefit of fondaparinux over heparin.[54,61] For all other patients receiving an invasive strategy, it appears that fondaparinux is at least as good an option, if not a better one, than either unfractionated or low-molecularweight heparin. These data support the recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for management of unstable angina and non-STEMI, in which fondaparinux is cited as a class I recommendation for either an invasive or a conservative management strategy.[1]

Importantly, the net clinical outcome was consistent with fondaparinux regardless of whether it was coadministered with other effective antithrombotic drugs (including thienopyridines and glycoprotein IIb/IIIa antagonists) and other therapies such as statins and blockers of the rennin-angiotensin system. Among patients undergoing PCI for ACS without ST-segment elevation and rescue, routine, or facilitated PCI for STEMI, fondaparinux reduced bleeding with similar rates of death, MI, or stroke compared with heparin.[54] The small absolute excess in catheter thrombus when fondaparinux was used as the sole anticoagulant (7 per 1000 patients) did not seem to translate into an increase in

clinical ischemic events between groups. This finding suggests that the reduction in bleeding with fondaparinux may have offset any increase in the risk of major events related to catheter thrombus. Furthermore, the risk of catheter thrombus was essentially eliminated when adjunctive UFH was administered in the catheterization laboratory immediately before the PCI procedure. At present, on the basis of limited experience in OASIS-5 and concerns raised by OASIS-6, UFH (50 to 60 U per kg IV) is recommended with a fondaparinux strategy during angiography/PCI.[1]

Future trials are therefore needed to identify the optimal dose of UFH to be used in fondaparinux treated patients. The Fondaparinux Trial With UFH During Revascularization in Acute Coronary Syndromes (FUTURA) OASIS 8 trial will randomize 2000 fondaparinux-treated ACS patients undergoing PCI to receive 2 doses of UFH (standard, activated clotting time guideline–recommended doses versus empirical low-dose UFH).[55]

Aggressive antiplatelet and anticoagulant therapies combined with an invasive strategy improve outcomes but also increase the risk of complications, including bleeding.[56,57,58]
Bleeding is prognostically important because it is associated with an increased risk of mortality as well as recurrent ischemic events. [59,63]

This highlights the importance of having antithrombotic treatments that are safe, easy to administer, less expensive, and that can be given to a broad range of patients with ACS.
As patients at very high or very low risk are usually excluded from clinical trials, it is critically important to determine whether new treatments show evidence of benefit across

the risk spectrum and whether there is net clinical benefit at all levels of risk when efficacy is balanced against bleeding.[60]

ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction [1]

ANTICOAGULANT THERAPY

CLASS I

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

a. For patients in whom an invasive strategy is selected, regimens with established efficacy at a *Level of Evidence: A* include enoxaparin and UFH, and those with established efficacy at a *Level of Evidence: B* include bivalirudin and fondaparinux.

b. For patients in whom a conservative strategy is selected, regimens using either enoxaparin or UFH *(Level of Evidence: A)* or fondaparinux *(Level of Evidence: B)* have established efficacy.

c. In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. *(Level of Evidence: B)*

CLASS IIa

For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG is planned within 24 h. (Level of Evidence: B)

It is suggested by ACC/AHA 2007 guidelines that each institution agree on an approved anticoagulant approach most consistent with local practice and preference.

Relevance of the present study

We conducted a preliminary study among our patients presented with UA/NSTEMI and who received enoxaparin, to find out the incidence of the primary outcome (the composite of death, myocardial infarction ad refractory ischemia at 1 month) and individual components of this composite.

The outcomes for this retrospective cohort of our patients who received enoxaparin were considerably less favorable than that obtained for enoxaparin recipients in the OASIS 5 trial, in spite of similarities in indications for use of enoxaparin. It would be prudent to conduct a systematic prospective evaluation of patients treated with fondaparinux to evaluate whether there are any differences in their outcomes compared to patients given enoxaprin in our retrospective cohort.

Fondaparinux is given once daily while enoxaparin is given twice daily. The costs of treatment between the two, for all brands of both drugs, favor fondaparinux.

This study is designed to assess the utility of fondaparinux in our current clinical practice.

METHODS

This is a prospective study to test the hypotheses that in the acute treatment of patients with unstable angina/ myocardial infarction without ST elevation, fondaparinux is safe and effective in preventing death, myocardial infarction or refractory ischemia.

The study was performed among patients from the cardiology department of Christian Medical College, Vellore; a tertiary care institute in South India.

The study protocol was approved by the institutional review board (IRB) and the ethics committee.

Study Patients

Patients who consent to participate in this trial were assigned to the study group within 48 hours after the onset of symptoms to receive fondaparinux at a dose of 2.5mg once daily subcutaneously, for a minimum duration of 5 days. With recurrence of angina within 5 days of treatment fondaparinux was continued and the need for early revascularization was re-emphasized. PCI could be done at any time and fondaparinux was stopped following PCI. Patients received other standard treatments as is clinically indicated. An early invasive strategy is offered to high risk patients and those who develop recurrent angina or re-infarction in spite of adequate medical management. In patients who received fondaparinux, 50 to 60 U per kg IV bolus of UFH is given during PCI.

Comparator: A preliminary study was conducted to find out the incidence of the composite outcomes and individual components of this composite, with enoxaparin. Consecutive inpatient and outpatient medical records of 44 patients who presented to the chest pain unit with unstable angina/NSTEMI who were given enoxaparin were analyzed.

The results of the record review are as follows: [1] The composite outcome of death, Non-fatal MI and refractory angina at 1 month was 34% (vs 8.6% in enoxaparin arm of OASIS-5). The individual outcomes a) death – 6.8% (vs 3.5% in OASIS) b) refractory ischemia – 27.2% (vs 2.2% in OASIS). [2] The rate of revascularization procedures was much lower in our population – (PCI/CABG at 30 day)- 27.2% (vs 54.2% in OASIS). [3] There were no documented major bleeding or stroke in 30 days period, among our patients. Thus, it is apparent that the outcomes in our patient population treated with enoxaparin differed from the patients given enoxaparin in the landmark (OASIS) trial, in many aspects in that patients in the enoxaparin arm in OASIS had better clinical outcome and more frequent revascularization procedures.

Historical controls were given enoxaparin 1 mg/kg twice daily [44 patients treated with enoxaparin]. In patients whose creatinine clearance was below 30 ml per minute, the enoxaparin dosage was reduced to 1 mg per kilogram once daily. Enoxaparin was given for two to eight days or until the patient was clinically stable, in an approach consistent with the current approval for its use in persons with unstable angina and myocardial infarction without ST elevation. All patients received other standard treatments.

Key inclusion /Exclusion Criteria

Inclusion Criteria:

Unstable angina as defined as angina pectoris or equivalent type of ischemic discomfort with at least one of 3 features:

a) Occurring at rest or with minimal exertion and usually lasting more than 20 min.

b) Being severe and frank pain and of new onset

c) Occurring with a crescendo pattern

Patients were assigned to study group within 48 hours after the onset of symptoms and were eligible if they met at least one of the two following criteria: 1) an elevated level of troponin or creatine kinase MB, 2) ECG changes indicative of ischemia. (ie, ST depression at least 1mm in 2 contiguous leads or T-wave inversion >3 mm or any dynamic ST shift or transient ST elevation)

Exclusion Criteria:

1. Contraindications to anticoagulation

2. Recent hemorrhagic stroke

3. Indications for anticoagulation other than an acute coronary syndrome

4. Serum creatinine level >3 mg/dl.

5. Severe hepatic failure

6. Any active major bleeding.

OUTCOMES

Primary outcomes:

A) Primary efficacy outcome: A composite outcome measure comprising of death/ nonfatal myocardial infarction/ refractory angina at 1 month

B) Primary safety outcome: major bleeding or stroke at 1 month

Secondary Outcomes:

Death, nonfatal myocardial infarction, refractory angina, stroke or major or minor bleeding at 1week and rate of revascularization within 1month.

Criteria for diagnosis of acute myocardial infarction

Detection of rise and/ or fall of cardiac biomarker (troponin) together with evidence of myocardial ischemia with at least one of the following:

1) Symptoms of ischemia
2) ECG changes indicative of ischemia (new ST-T changes or new LBBB)
3) Development of pathological Q waves in ECG
4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

When recurrent myocardial infarction was suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of troponin was done. A second sample was obtained 3–6 h later. Recurrent infarction was diagnosed if there is a more than or equal to 20% increase of the value in the second sample.

PCI related MI was diagnosed with an increase of biomarkers > 3x99th percentile of upper reference limit (URL).

CABG related MI was diagnosed with an increase of troponin >5x99th percentile of URL plus either new Q waves or new LBBB or imaging evidence of new loss of viable myocardium.

Refractory ischemia is defined as recurrent ischemic symptoms lasting more than 5 minutes while on optimal medical therapy with ECG changes indicative of ischemia and requiring an additional intervention within 48 hours (revascularization procedure).

Classification of hemorrhagic events:

TIMI major bleeding involves a hemoglobin drop >5 g/dL (with or without an identified site) or intracranial hemorrhage or cardiac tamponade.

TIMI minor bleeding involves a hemoglobin drop >3 g/dL but ≤5 g/dL, (with or without an identified site) or spontaneous gross hematuria, hemoptysis, or hematemesis.

Patients were followed up for 30 days.

Statistical Analysis

Target sample size calculation and rationale:

The sample size was calculated using the rates of clinical endpoints of treatment with enoxaparin from the historical data and the expected reduction in the incidence of events by using the drug fondaparinux. The study is sufficiently powered for to demonstrate superirority of fondaparinux for the primary outcomes.

Calculation of sample size - formula used: $n = (Z\ alfa + Z\ beta)^2 x 2pq/(p1-p2)^2$,

p1 = 34%(primary endpoint in the historical control), p2 = 8.0% (primary endpoint in the landmark trial), p = p1+p2/2 , q =100-p. n = 40 in each arm.

RESULTS

A total of 40 patients were studied.

Table 1 shows the baseline characteristics of the patients

The mean age of the patients was 63.4 +/- 9.3 years; they were predominantly male (73%). Majority were diabetic patients 31(77.5%) and 15 (37.5%) patients had suffered a previous ST elevation myocardial infarction.

Mean duration of symptoms before presentation to hospital was 7 hours with a minimum of 2 hours and maximum of 42 hours.

The mean duration of treatment was not similar in the 2 groups (5 days in fondaparinux group and 3 days in the enoxaparin group. The minimum duration of treatment with fondaparinux was 2 days and a maximum of 8 days. Extended duration of antithrombotic therapy was given to patients who developed refractory ischemia.

Table 1 Patient characteristics

Variable	Number (%)
Age (yrs)	63.4 +/- 9.3
Male	29(73%)
Diabetes mellitus	31(77.5%)
Previous MI	15(37.5%)
Previous PCI/CABG	4(10%)
Mean duration of symptoms (hrs)	7
Unstable angina	20(50%)
NSTEMI	20(50%)
Any ECG abnormality	37(92.4%)
Patients with GFR<60 ml/min	7(17.5%)
LV systolic dysfunction	26(65%)

An early risk stratification using Thrombolysis In Myocardial Infarction (TIMI) risk-stratification model was done for all patients included in the study. Thirty one patients (77.5%) had a risk score of three or higher and these patients were offered an early invasive strategy. But only 2 patients (5%) had undergone PCI during the index hospitalization.

Table 2 TIMI risk scoring

Variable	Number (%)
TIMI low risk	9(22.5%)
TIMI intermediate risk	20(50%)
TIMI high risk	11(27.5%)

Primary outcomes

The primary efficacy outcome (the composite of death, myocardial infarction, or refractory ischemia at 30 days) occurred in 11 (27.5%) of the 40 patients who received fondaparinux as compared with 15 (34%) of the 44 patients in the retrospective cohort who received enoxaparin. The difference in rate of the primary efficacy outcome observed in this study was not statistically significant (p= 0.51). This difference was primarily due to a non-significant reduction in mortality and refractory ischemia with fondaparinux.

The rates of individual outcomes at 30 days (death or refractory ischemia) in 2 groups were analyzed. The difference in the rates of death (5.0 percent in the fondaparinux group and 6.8 percent in the enoxaparin group P = 0.72) or the refractory ischemia (22.5% in the fondaparinux group and 27.2% in the enoxaparin group; p = 0.61) at 30 days was not statistically significant. There was no documented myocardial infarction in either group during the 1 month follow up period.

Figure 1 Primary outcome at 30 days (p=0.51)

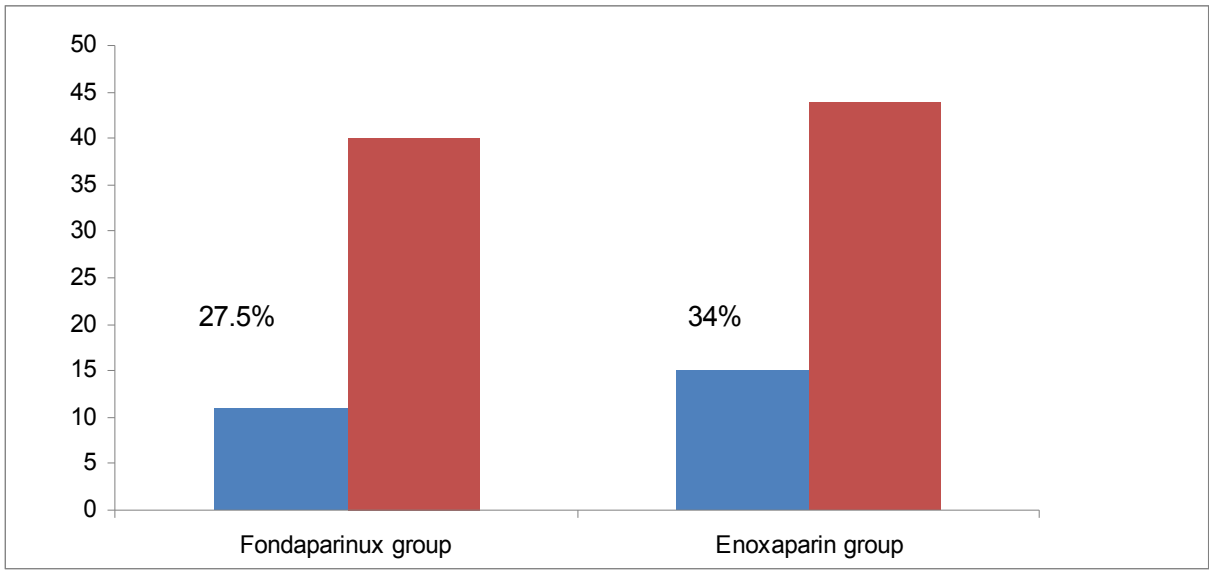


Figure 2 Death at 30 days

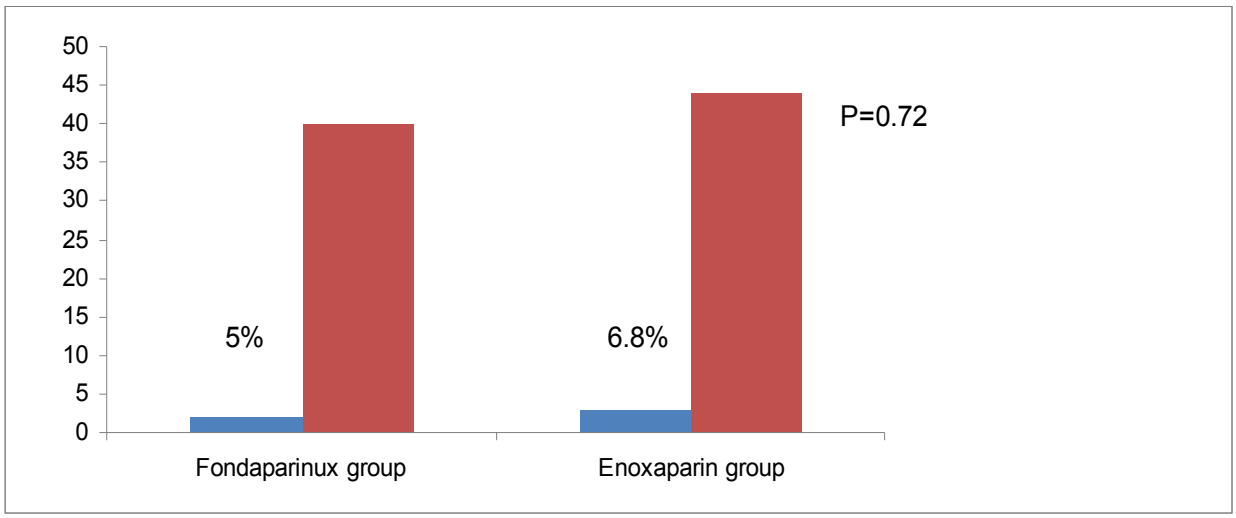
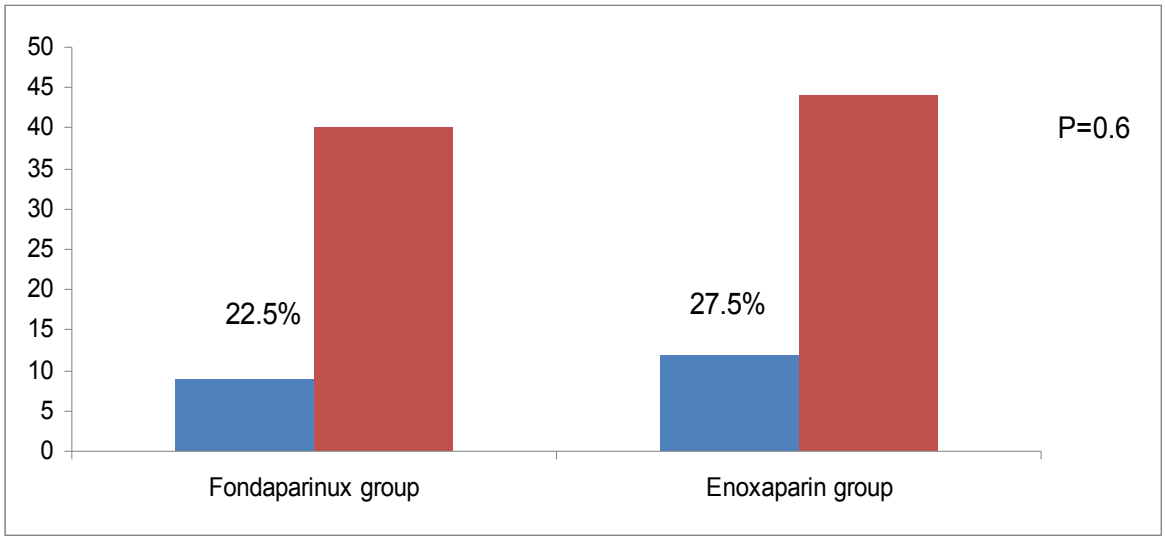


Figure3. Refractory ischemia at 30 days



Primary safety outcome

In our study there was no documented stroke or major bleeding either in patients received fondaparinux or in those received enoxaparin.

Outcomes at 1 week

The rate of composite clinical outcome at 1 week was not significantly different between the 2 groups (15% in the fondaparinux group and 18% in the enoxaparin group). There was a non-significant trend toward a lower rate of death at one week in the fondaparinux group. There were no deaths in week in fondaparinux group, but 3 patients died in the enoxaparin group at 1 week. This difference mortality was not statistically significant (p= 0.09). Totally 2 patients died in the fondaparinux group, both between 20^{th} and 30^{th} day.

Revascularization procedures

The rate of revascularization procedures (PCI/ CABG) at 1 month was almost similar in the 2 groups (22.5% in the fondaparinux group and 27.2% in the enoxaparin group). There were no procedure related complications either in patients who underwent PCI during the index hospitalization or those who had PCI within 1 month. Heparin was given during PCI for patients who received fondaparinux.

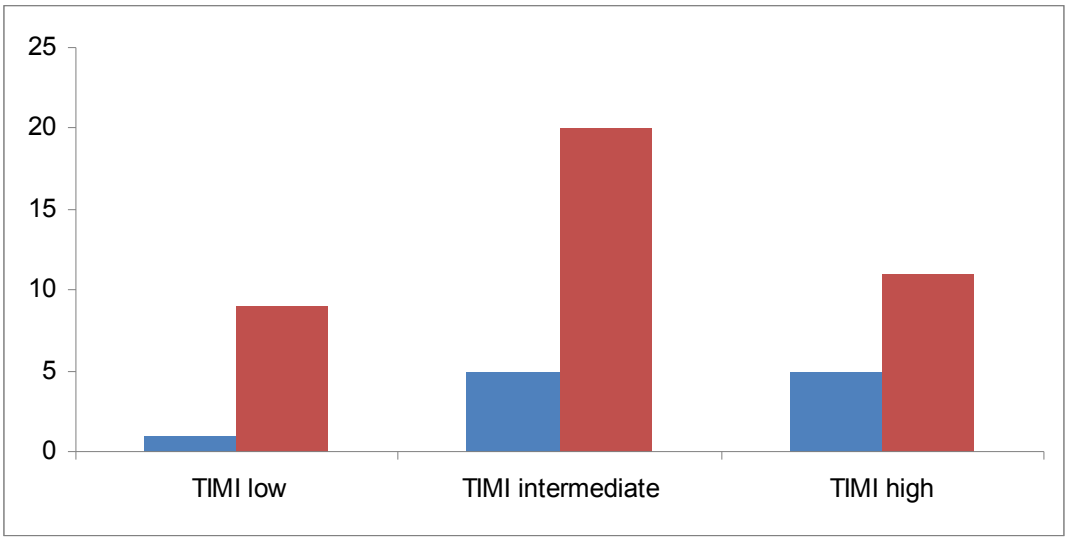
Table 3 Efficacy outcomes

Time and outcome	Fondaparinux (N = 40)	Enoxaparin (N = 44)	P value
	Number (%)	Number (%)	
1 week			
Composite (death,MI,RI)	6 (15%)	8 (18%)	0.69
Death	Nil	3 (6.8%)	0.09
MI	Nil	Nil	
Refractory ischemia	6 (15%)	5 (11.4%)	0.71
1 month			
Composite (death,MI,RI)	11 (27.5%)	15 (34%)	0.51
Death	2 (5%)	3 (6.8%)	0.72
MI	Nil	Nil	
Refractory ischemia	9 (22.5%)	12 (27.2%)	0.61
1 month PCI/CABG	9 (22.5%)	12 (27.2%)	0.61

Subgroup analysis

As expected the rate of primary efficacy outcome was higher in TIMI high and intermediate risk groups than the low risk group (composite outcome occurred in 11.1% of patients in TIMI low risk group, 25% of patients in intermediate risk group and 45.5% of patients in the high risk group).

Figure4. Primary outcome in TIMI subgroups



LV systolic dysfunction

Out of 40 patients 26 (65%) had LV systolic dysfunction by echocardiogram (ECHO).

The primary composite outcome occurred in 9 out of 26 patients with LV systolic dysfunction (34.6%) while only 2 out of 14 patients without LV systolic dysfunction had the outcome (14.3%).

Renal failure

GFR was calculated using the modified MDRD formula. Seven out of 40 patients in the fondaparinux group had GFR less than 60ml/min. The rate of primary composite outcome at one month was significantly higher in patients with renal failure than in patients with normal renal function (57% versus 21.2%, p=0.05).

Medications at discharge and at 1 month

The mean duration of hospital stay was two days. At discharge all patients were on double antiplatelets and a statin. More than 90% of the patients were on betablocker and ACE inhibitor/ARB at discharge. At one month only 70% of the patients were on regular medications as advised at the time of discharge or at 1 week follow up. Rest of the patients stopped taking all drugs at the time of review after one month.

DISCUSSION

In this study we have evaluated the utility of fondaparinux in management of patients with unstable angina/ NSTEMI, in our current clinical practice.

The effect of fondaparinux versus enoxaparin on the primary composite outcome of death, myocardial infarction, and refractory ischemia at 30 days was similar (27.5% versus 34% p=0.51) and the differences in rates of death and refractory ischemia at 30 days between the 2 groups were also statistically not significant.

Surprisingly, there were no documented bleeding or stroke in either fondaparinux or enoxaparin group during the study period.

The OASIS-5 (Organization to Assess Strategies in Ischemic Syndromes-5) trial demonstrated that fondaparinux was non-inferior to enoxaparin while reducing the risk of bleeding by 50%.[8] Bleeding increased the long term risk of death. In addition, there were significantly fewer strokes with fondaparinux than with enoxaparin. Therefore, the OASIS 5 trial showed a net clinical benefit clearly in favor of fondaparinux.

Several previous studies have found increased rates of death, stroke, and myocardial infarction among persons who had a bleeding episode.[59,63]

There was no documented bleeding in our patient population. Though the rate of primary composite outcome was higher in patients with renal failure than in patients with normal renal function, there was no bleeding in this group of patients with increased bleeding risk. Similarly there was no bleeding in elderly patients (10 patients in the fondaparinux group were 70 years or above).

The absence of major bleeding and stoke in our study population could be due to small number of patients and that could also explain the reason for the lack of benefit of fondaparinux over enoxaparin. In the OASIS 5 trial, the difference in bleeding appeared to account for the reduction in the long term risk of death with fondaparinux. Therefore a larger study is needed to prove the benefits of fondaparinux in our patient population. In patients undergoing PCI, the contemporary practice of using double antiplatelets, loading dose of clopidogrel and glycoprotein IIb/IIIa inhibitors might lead to more bleeding complications. Less number of coronary interventions in our study could be another reason for lack of bleeding.

By comparing our study results with landmark trial (OASIS 5) we found that the rate of composite of death, myocardial infarction or refractory ischemia at 1 month, in our study was substantially higher than those rates in the OASIS 5 trial (27.5% versus 8.0%, p= <0.001). Similarly the rate of refractory ischemia was significantly higher in our population (22.5% versus 2.2%,p=<0.001). But the difference in the rate of death at month was not statistically significant.

The higher rate of outcomes in our study was primarily due to a higher rate of refractory ischemia. This difference in the outcomes was observed, in spite of similarities in indications for use of the anticoagulant therapy. While analyzing the outcomes of our retrospective cohort we found similar results .

Similarly the rate of revascularization procedures at 1 month was significantly less in our patient population compared to OASIS population (22.5% versus 54.2%, p= <0.001).

In spite of clear indications for immediate coronary angiogram and revascularization, in many of our high risk patients, early PCI was done only in a small number of patients.In (TACTICS) TIMI 18 trial, the TIMI risk score was used to assess the benefit of an early invasive strategy.[26] A significant benefit with invasive strategy was observed in patients with a risk score of 3 or higher. Thirty one (77.5%) patients in our study had a TIMI risk score of 3 or higher. Out of these 31 patients only 2 patients underwent early PCI. This could be an important explanation for higher rate of refractory angina seen in our study.

When compared to OASIS 5, though there were significantly higher rates of refractory angina in our study, the rates of death or MI were not significantly different. In spite of more frequent revascularization procedures in OASIS 5, there was no significant reduction in major irreversible cardiovascular events (death/ MI) when 2 studies are compared. Thus the patients treated with a more aggressive approach were at lower risk of refractory angina or readmission for unstable angina.

At the time of discharge almost all of the patients were on double antiplatelets, betablocker, ACE inhibitor/ ARB and a statin but only 70% of the patients continued all medications till the end of 1 month . About 30% of the patients were not on appropriate cardiac medications at 1 month. This poor patient compliance in our population is one of the most important factors leading to more frequent complications.

When we analyzed the rate of composite outcomes in patients those who were not on regular medications, showed a higher rate than those who were on regular medications (41.7% in patients who stopped medications and 21.4% in patients who were on regular medications). But this difference in the rate was not statistically significant (p=0.19). We acknowledge that the sample may be underpowered to detect significant differences in subgroup analyses but will provide indicative data.

Thus, it is apparent that the outcomes in our patient population treated with either fondaparinux or enoxaparin differed from the patients in the landmark (OASIS) trial, in that patients in the OASIS trial had better clinical outcome and more frequent revascularization procedures.

The poorer clinical outcome in our population could be due to

1) Late presentation and early discharge from the hospital

2) Non-adherence to medications

3) Less frequent revascularization procedures (early PCI/CABG) even when indicated

4) Lack of regular follow up

The basic reasons for the above mentioned observations are financial constraints and lack of awareness among our patients.

Advantages of fondaparinux over enoxaparin

For management of patients with unstable angina/NSTEMI, fondaparinux have established efficacy. Fondaparinux with single daily dosage, promises better patient compliance

especially when it has to be continued even after discharge from the hospital. Being once daily dosage the cost of treatment with fondaparinux much less than that of enoxaparin. Therefore, fondaparinux is an effective, less expensive, and safe antithrombotic agent for treatment of patients with UA/NSTEMI.

LIMITATIONS

1) The number of patients studied was limited and the duration of follow up was short. The findings need to be confirmed in a larger population of patients for a longer period of time.

2) As the control was retrospective cohort, the present study was limited by lack of randomization, incomplete data of the retrospective group, and the differences in the baseline patient characteristics between the two groups.

These limitations should be considered in the interpretation of its results.

SUMMARY OF MAIN FINDINGS

1) The impact of fondaparinux versus enoxaparin in preventing the death, myocardial infarction, and refractory ischemia in patients with unstable angina/NSTEMI at 30 days was similar.

2) In our study there was no documented stroke or major bleeding either in patients received fondaparinux or in those received enoxaparin probably because of the small number of patients and less number of coronary revascularization procedures. The absence of bleeding and stroke could explain the lack of benefit of fondaparinux over enoxaparin.

3) There was a non-significant reduction in mortality with fondaparinux, at 1 week.

4) The outcomes in our patient population treated with either fondaparinux or enoxaparin differed from the patients in the landmark (OASIS) trial, in that patients in our study had more frequent hospitalizations for refractory ischemia. This could be explained by less number of revascularization procedures.

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PROFORMA

Name:

Age: Sex:

Hospital number:

Occupation:

Address:

Phone number:

Presenting complaints: Chest pain –no (0)/yes(1)
dyspnoea – no(0)/yes(1)/
other symptoms– no(0)/yes(1)
Duration of symptom prior to presentation

Two or more than two anginal episodes in prior 24 h – no(0)/ yes(1)

Heart failure symptoms at presentation – no(0)/ yes(1)

Pulmonary edema at presentation (settled without ventilatory support)- no(0)/ yes(1)

Pulmonary edema requiring ventilatory support – no(0)/ yes(1)

Risk factors:

Age >/= 65yrs – no(0)/ yes(1)

Diabetes mellitus – no(0)/ yes(1)

Three or more than three CAD risk factors – no(0)/ yes(1)

Prior CVA – no(0)/ yes(1)

Known CAD (50% stenosis)

Aspirin within prior 1 week

Post MI angina – no(0)/ yes(1)

Secondary angina – no(0)/ yes(1)

Previous myocardial infarction – no(0)/ yes(1)
Anterior wall MI – no(0)/ yes(1)
LV dys – no(0)/ yes(1)

Prior PCI – no(0)/ yes(1)
Year-
Within 1 month – no(0)/ yes(1)
BMS (1)/ DES (2)
Indication – ACS (1)/ stable angina (2)

Prior CABG – no(0)/ yes(1)
Year

Prior history of stable angina : no(0)/ yes(1)

Physical findings (at presentation):
Pulse:

BP:

Cardiogenic shock during hospital stay – no(0)/ yes(1)

Cardiac arrest – resuscitated (during hospital stay) – no(0)/ yes(1)

S3 or new/worsening rales – no(0)/yes(1)

New or worsening MR murmur – no(0)/yes(1)

ECG changes:
ST depression more than or equal to 0.5mm
T inversion more than or equal to 0.3mv
Bundle branch block –new or presumed new – no(0)/ yes(1)
Sustained VT – no(0)/ yes(1)
No ECG changes

Cardiac markers:
Increased Trop I or CK-MB – no(0)/ yes(1)

ECHO:
RWMA- no(0)/ yes(1)
MR- no(0)/ yes(1)
LV dysfunction - no(0)/ yes(1)

GFR <60ml/min– no(0)/ yes(1)

Events in 1 week:

Death
- Immediate cause of death
- Time interval between presentation and death
- PCI done or not
- Co-morbidities

Recurrence of angina after the initiation of treatment
- Time interval from initiation of treatment
- Treatment received for refractory angina

Re- infarction
- Time interval from initiation of treatment
- Treatment received for re-infarction

Bleeding - no(0)/ yes(1)
- Minor bleeding- no(0)/ yes(1)
- Major bleeding – no(1)/yes(1)
- Managed by –

Stroke - no(0)/ yes(1)
- Time interval after initiation of treatment

PCI in 1 week
- Ischemia driven - no(0)/ yes(1)
- Other indications
- Angiogram findings
- BMS/DES
- GP IIb/IIIa
- Post- PCI events

CABG in 1 week – indication
- Time interval between presentation and surgery

Duration of hospital stay

Treatment received:

Aspirin – no(0)/ yes(1)
Clopidogrel – no(0)/ yes(1)
Statin – no(0)/ yes(1)
Betablocker- no(0)/ yes(1)
ACEI/ARB -- no(0)/ yes(1)

Fondaparinux:
- No. of days of treatment with fondaparinux – 5 days (1)/ more than 5 days(2)

Follow up visit at 1 week - no(0)/ yes(1)

30 day events:

Death
Immediate cause of death
Time interval between initial event and death
PCI done or not
Co-morbidities

Recurrence of angina after completion of treatment with fondaparinux
Time interval after completion of treatment with fondaparinux
Treatment received for refractory angina
Re- infarction
Time interval after completion of treatment with fondaparinux
Treatment for re-infarction
Bleeding - no(0)/ yes(1)
Time interval after completion of treatment with fondaparinux

Minor bleeding- no(0)/ yes(1)
Major bleeding – no(1)/yes(1)
Managed by –
Stroke - no(0)/ yes(1), time interval after completion of treatment with fondaparinux
PCI within 30 days
Ischemia driven - no(0)/ yes(1)
Other indications
Angiogram findings
BMS/DES
GP IIb/IIIa
Post- PCI events
CABG within 30 days– indication
Time interval between presentation and surgery

Follow up visit at 30 day - no(0)/ yes(1)

Glossary for master chart

hospno	hospital number
duration	duration of symptoms
puledma	pulmonary edema
tottimi	total TIMI score
timilow	TIMI low risk
timiinter	TIMI intermediate risk
timihigh	TIMI high risk
priormi	prior myocardial infarction
priorvasc	prior revscularization
dm	diabetes mellitus
ecgchang	ECG changes
Ua_nstem	admission diagnosis – UA/NSTEMI
wk1comp	composite endpoints at 1 week
wk1death	death at 1 week
wk1MI	myocardial infarction at 1 week
wk1ri	refractory ischemia at 1 week
mon1comp	composite endpoints at 1 month
mon1death	death at 1 month
mon1mi	myocardial infarction at 1month
mon1ri	refractory ischemia at 1 month
inhopproc	procedure during the index hospitalization
pciwk1	PCI in 1 week
pcimon1	PCI in 1 month
cabg	CABG
renalfail	renal failure
lvdys	LV dysfunction
asp1w	aspirin at 1week
clop1w	clopidogrel at 1 week
bb1w	betablocker at 1 week
ace1w	ACEI/ARB at 1week
stat1w	statin at 1 week
asp1m	aspirin at 1month
clop1m	clopidogrel at 1 month
bb1m	betablocker at 1 month
ace1m	ACEI/ARB at 1month
stat1m	statin at 1 month
1	male
2	female
each variable	If Yes (1)
	If No (0)
1	Ua (unstable angina)
2	NSTEMI